REMARKS

Rejection of Claims and Traversal Thereof

In the February 4, 2008 Office Action:

claim 13 was rejected under 35 U.S.C. §112, first paragraph;

claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. §103(a) as being unpatentable over Kuo et al, (WO 98/04272, hereinafter Kuo) in view of Wittmann et al, (Peptides: The Wave of the Future, 2001 pages 174-176, hereinafter Wittmann) and Maddon et al. (WO 00/18432, hereinafter Maddon.).

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under 35 U.S.C. §112, first paragraph

Claim 13 was rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. Applicant disagrees because the immunogenic protein keyhole limpet hemocyanin is a well known immune modulator that is known to enhance an immune response.

The Office states that there is no teaching or guidance in the specification that would lead one of ordinary skill in the art to expect the KLH construct to induce an immune response that can reduce HIV infectivity. Applicant insists that it is well known to those skilled in the art that Keyhole limpet (Megathura crenulata) hemocyanin (KLH) is widely used as an immune system stimulant in the generation of antibodies. It is also known that antibodies to small peptides or haptens are typically produced by conjugating them to large carrier proteins such as KLH. The conjugate is used to immunize an appropriate animal host species such as mouse, rabbit or goat. The host will produce antibodies against the peptide/hapten as well as to the KLH. KLH has several desirable properties which makes it a good choice as a carrier protein. KLH has an immunostimulatory capacity similar to other commonly used carrier proteins such as ovalbumin (OVA) and bovine serum albumin (BSA). It is well known that antibodies raised against KLH do not interfere with antibodies raised against the high-mannose oligosaccharide cluster. Importantly because the high-mannose oligosaccharide clusters of the present invention mimic a conserved epitope on gp120, the inclusion of KLH can

enhance the immune response, that being an increase in antibodies that can bind to the conserved epitope on gp120.

The present specification provides instructions for all the steps required for producing the high-mannose oligosaccharide clusters and the use of same. Thus, the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, and the specification need not disclose what is well known in the art. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984). It has been consistently held by the courts that the first paragraph of 35 USC §112 requires nothing more than objective enablement. In satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well-known in the art. Clearly if every last detail needed to be described, a patent specification would turn into dissertation, which they were never intended to be.

Applicant submits that the instant application provides sufficient and enabling information for a person of ordinary skill in the art to practice applicant's invention and respectfully requests the withdrawal of all rejections under §112, first paragraph.

Rejection under 35 U.S.C. §103(a)

Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. §103(a) as being unpatentable over Kuo in view of Wittmann and Maddon. Applicant insists that the proposed combination does not in any way render the presently claimed invention as obvious.

Kou describes the determination of mannose complexes that are part of the major outer membrane protein (MOMP) which is the principal structural protein of the elementary body (EB) of Chlamydia. MOMP includes carbohydrate moieties that are instrumental in the attachment of the Chlamydia to host cells. The main purpose of Kou, as stated above, is determining the possible structures of such carbohydrates. Figure 1 and Table 3 of the Kou reference show that the oligosaccharides released from the MOMP glycoprotein include not only high-mannose type but also complex type species. These structures were determined by multiple assays and antibody studies. Clearly, there is no guidance as to which of the oligosaccharides are important for building of the MOMP structure to interact with a host cell. Table 4 shows that an oligomannose 8 was the most effective, however, it should be noted that Kuo used only a single carbohydrate chain. Applicant understands that this reference discusses the use of a scaffold for placement of the carbohydrates but provides no guidance

for generating a carbohydrate moiety that mimics an epitope on gp120 and that can interact with 2G12 antibodies, as in the presently claimed invention.

According to the Office, Wittmann has used cyclic peptides as scaffolding for multivalent presentation of carbohydrate epitopes, and thus, there would be a reasonable expectation of success given the knowledge of others to use a cyclic core. Applicant disagrees.

Wittmann describes carbohydrate-lectin interactions because high-affinity lectin ligands are of considerable medicinal interest in therapy and prevention of diseases. Wittmann is attempting to synthesize such carbohydrate epitopes that interact with the targeted lectins and describe the use of a library of spatially diverse mini clusters to determine the carbohydrate structure with the most activity towards the targeted lectins. To produce this library, Wittmann uses a cyclic peptide with amino acid points of attachments for the carbohydrates. The cyclic peptide has 6 places of attachments with different stereochemistry and numerous possibilities for combinations of patterns displayed on the scaffold.

Notably, the attaching group to the lectin ligands is always a single GlcNAc molecule and there is no discussion for introducing different carbohydrate moieties. Yes the cyclic peptide can include multiple GlcNAc groups at different amino acids but there is no suggestion to change the GlcNAc group to a high mannose group.

Applicant insists that the Office has arbitrarily isolated a single element from the Kou disclosure, namely a high mannose oligosaccharide, and then attempted to combine with the teachings of Wittmann. However, it is very evident that neither reference provides any guidance to recreate the oligosaccharides into a pattern that resembles an epitope on HIV gp120 which interacts with 2G12 antibodies.

Wittmann talks about the possibility of forming exactly 19,440 different compounds by using a permutation for all the possibilities of numerous attachments to the different amino acids. Further, Kuo isolated seven different types of oligosaccharide structures.

According to the Office:

> "it would have been obvious to attach four or more high-mannose structures to a common carrier to create multivalent structures with enhanced avidity for a ligand and thus inhibit binding much more effectively as taught by Wittmann."

Initially it must be recognized by the Office that Wittmann does not state that placement of four or more structures increases affinity. Instead it only states that four specific sites were conserved and additional studies needed to be conducted. Wittmann speculated that placement of the GlcNAc residues are responsible for different binding affinities. There is no way to know whether the four conserved D-Dab(R) added to the affinity or was detrimental and the negative binding was overcome by the placement of additional GlcNAc residues. Thus four is not a magic number in Wittmann.

Applicant is well aware that Kuo has shown that **A SINGLE** oligomannose 9, supposedly mimics the carbohydrates of MOMP and exhibited a 64/62 % inhibition, but there is no guidance that such a mannose would be effective as a mimic of an epitope on gp120. Notably, the secondary structure of the MOMP protein was first determined in 1988 by Baehr, et al. (1988) Proc. Natl. Acad. Sci. USA.; Vol. 85, pp. 4000-40004 and includes a group of beta strands aligned parallel to each other and recreated below

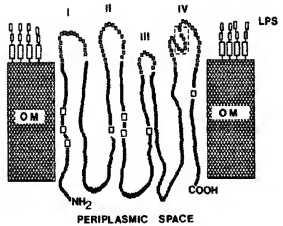
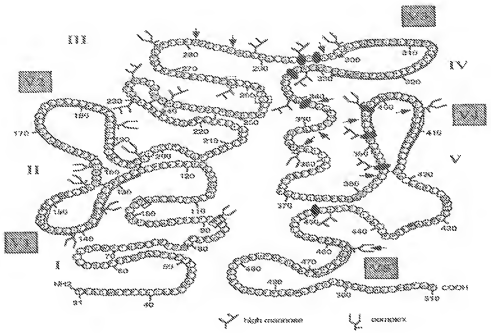


FIG. 5. Scheme of MOMP in the outer membrane layer of the chlamydial cell wall. Solid line, membrane-embedded peptide chain of MOMP (not drawn to scale with respect to thickness of membrane or size of VDs); small open squares, residues comprising the VDs; large open squares, conserved cysteines; broken box within VDIV, species-specific epitope L2I-10 common to all MOMPs. The presence of lipopolysaccharide structures (LPS) in chlamydiae is indicated above the outer membrane (OM).

It is difficult for applicant to believe that one skilled in the art knowing the structure of the MOMP would really even consider that a carbohydrates structure that mimics MOMP would give any

guidance for a carbohydrate structure that mimics an epitope of gp120. Applicant provided in the present application the secondary structure of gp120 which is reproduced from Trkola, as shown below:



Clearly, the structure of gp 120 and MOMP are so entirely different that one skilled in the art would not gain any guidance from Kuo alone or in combination with Wittmann. There are so many possibilities regarding the types of carbohydrates and the number of such carbohydrates on a scaffold that these references provide no guidance for applicant's claimed invention.

Notably, the Federal Circuit recently addressed this very issue and applicant refers the Office to the post-*KSR* case of *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, No. 2007-1223 (Fed. Cir. 2008), where the Court determined that such a large number of possibilities does not provide sufficient guidance for the carbohydrate complex of the pending claims.

In *Ortho-McNeil*, the validity of a patent covering the drug topiramate was challenged by the infringer as being invalid because of obviousness. The infringer cited *KSR* for the proposition that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." The *Ortho-McNeil* Court rejected this line of argument by stating that

"[T]his invention, contrary to [plaintiff's] characterization, does not present a finite (and small in the context of the art) number of options easily traversed to show obviousness. The passage above in *KSR* posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of the obviousness. "

The *Ortho-McNeil* Court further stated that an ordinarily skilled artisan would have to have some reason to select (among several unpredictable alternative) the exact route to stop at the specific compound. The *Ortho-McNeil* Court stated that a large number of possibilities dose not fit into the ruling of a *KSR* criteria that was decided because of a small and finite number of alternatives.

Also the *Ortho-McNeil* Court reemphasized the flexible teaching, suggestion or motivation (TSM) test of *KSR*, wherein the *KSR* Court expressly stated that a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis such as the Office is using in the presently claimed invention. The Supreme Court suggested that a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of invention. A similar situation exists in the present case.

Notably, the statement by the Office that "One would have been motivated to do so given the suggestion by Kuo et al. to link high mannose structures to a common carrier . . . There would have been a reasonable expectation of success given the knowledge that others, such as Wittmann et al., have used cyclic peptides as scaffolding for the multivalent presentation of carbohydrate epitopes." has been completing dismissed as acceptable reasoning for establishing a case of obviousness by the *Ortho-McNeil* Court in situations were there are a multiplicity different structures. Specifically the *Ortho-McNeil* Court stated that "...the ordinarily skilled artisan would have to have some reason to select (among several unpredictable alternatives)."

It appears that the Office, **with hindsight**, has discounted the number and complexity of the alternatives, and concluded that the current invention is obvious. Of course, this reasoning is always inappropriate for an obviousness test based on the language of Title 35 that requires the analysis to examiner "the subject matter as a whole" to ascertain if it "***would have been obvious at the time the invention was made.***" 35 U.S.C. §103(a) (emphasis added). As stated in *Ortho-McNeil*,

> "In retrospect, [the Examiner's] pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of the invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even

serendipity, cannot be discounted" (see *Ortho-McNeil* at page 10, lines 9-12).

Moreover, the Kuo reference clearly states that the carbohydrates on the MOMP show different activity. Specifically Kuo states the inconsistency of binding as discussed in paragraph [0015], and recreated below:

> The carbohydrate moiety of MOMP binds ConA, wheat germ agglutinin (WGA) and *Dolichos biflorus* agglutinin; but does not bind to lectins from *Ulex europaeus* agglutinin, soybean agglutinin or *Ricinus communis* agglutinin. Thus, it appears that N-acetyl galactosamine (GalNAc), galactose (Gal) or fucose (Fuc) is not present or not exposed on MOMP.

As such, if there is this much inconsistency with binding of MOMP with different types of agglutinin then one skilled in the art or the Office could not possibly believe that Kuo teaches or provides guidance for any structure that will resemble a structure that interacts with 2G12 antibodies based on the text in Kuo.

Applicant has also found that the carbohydrates structures of the presently claimed invention have shown an unexpected high level of effectiveness. Reviewing the specification and specifically the results set forth on pages 34 and 35, such effectiveness of the presently claimed structures is evident, as recreated below:

> Binding of the synthetic Man_9-clusters to 2G12
>
> The synthetic Man_9-clusters were examined for competitive inhibition of 2G12 binding to immobilized gp120 (Figure 16). A significant clustering effect was observed for the Man_9-clusters as shown in Table 1 below.
>
> Potency on carbohydrate inhibition of 2G12 binding to gp120

Carbohydrate antigens	IC 50	Relative Affinity	
	(nM)	Molar basis	Valency-corrected
$Man_5GlcNAc$	200 estimated	0.004	0.004
$Man_8GlcNAc$	70	0.012	0.012
$Man_9GlcNAc$	0.98	0.84	0.84
$Man_9GlcNAc2Asn$	0.82	1.0	1.0
Man9-dimer	0.40	2.1	1.0
Bi-Man9	0.13	6.3	3.2
Tri-Man9	0.044	18.6	6.2
Tetra-Man9	0.013	63.1	15.8

If IC_{50} is taken as an indication for relative affinity (Table 1), the Tetra-Man_9 was found to inhibit the 2G12 binding 63-fold more effectively than monomeric $Man_9GlcNAc_2Asn$ does on a molar basis. This corresponds to a 16-fold increase in the affinity to 2G12 for each oligosaccharide subunit in Tetra-Man_9 on a valence-corrected basis, when compared with monomeric Man_9. On the other hand, the trivalent cluster Tri-Man_9 was 19-fold (on a molar basis) or 6-fold (on a valence-corrected basis) more effective than $Man_9GlcNAc_2Asn$ in inhibition of 2G12 binding to gp120.

It is evident that Kuo alone or in combination with Wittmann lacks any indication relating to which structure has the ability to mimic an epitope on gp 120 with affinity for the antibody 2G12 or provide the results shown by applicants.

Applicant insists that after a review of the new guidelines for determination of obviousness and recent relevant case law, the Office cannot establish a *prima facie* case of obviousness and as such, applicant requests that the rejection under 103(a) be withdrawn.

Claim 2 was rejected under 35 U.S.C. §103(a) as being unpatentable over Kuo and Wittmann in further view of Maddon. According to the Office, Kuo does not teach conjugating the high-mannose structures to an immunogenic protein. Maddon teaches that the immunogenicity of purified carbohydrates can be improved. Regardless of the teaching of Maddon, applicant respectfully submits that the defects in the alleged *prima facie* case with Kuo and Wittmann are not cured by the addition of Maddon. Applicant requests that the rejections under section 103(a) be withdrawn.

Fees payable

It is believed that no fees are due at this time. However, if a fee is found due, the Commissioner is hereby authorized to charge any deficiencies, or reimburse any over-charges, to Deposit Account No. 13-4365 of Moore & Van Allen, PLLC.

Conclusion

Applicant has satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Kinsey-White reconsider the patentability of the pending in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Kinsey-White is requested to contact the undersigned attorney at (919) 286-8089 to resolve same.

Respectfully submitted,

MOORE & VAN ALLEN PLLC

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By:_____

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